

**ASSESSMENT OF THE FUNCTIONING OF THE “CLINICAL TRIALS DIRECTIVE” 2001/20/EC
PUBLIC CONSULTATION PAPER**

A RESPONSE

Respondent:

Contact: c.roy-toole@btconnect.com

Christopher Roy -Toole

Barrister

Member UK NHS Research Ethics Committee NNT1

This is a private submission . Within the terms of the consultation on the Clinical Trials Directive, I have confined my responses to those questions that engage my experience directly as a lawyer and member of an ethics committee . This submission should be treated as an invitation to further enquiry rather than a definitive statement in itself. In expressing my opinions, I have cited published research relevant to my submissions, but time constraints have prevented me from making a systematic review of the literature and I do not have access at this time to operational research or costing data. If the Commission were minded to explore my recommendations in greater detail, this additional research would be required.

The format of my submissions follows its own order , and not the order of the issues raised by the consultation . But my submissions do address the key issues raised by the consultation. So it is necessary for the reader to extract topics of relevance from this document and match them to the questions in the consultation. To assist in this, I provide an index of topics and sub -headings and a summary of conclusions .

My submissions extend beyond the present consultation to embrace issues relevant to the current European Commission consultation on the future of the Data Directive ¹. These issues are linked and so they should be considered within each of the two consultations of the Commission .

¹ http://ec.europa.eu/justice_home/news/consulting_public/news_consulting_0003_en.htm

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The functional separation of Ethics Committees and Competent Authority: a case for combining them in a new Regulatory Authority for Clinical Trials

1. The question of the separation of function between National Competent Authority [NCA] and Research Ethics Committees [REC] is central to this consultation and to any resulting recommendations for future reform. The questions posed in this consultation document seem to presume that a clearer separation of responsibilities and functions between NCA and REC will lead to a more efficient service and will better enable a platform for future harmonization.
2. I contend that the reverse may be the case. Greater functional separation between REC and NCA might compromise the quality of ethical review, and its speed, and allow for adverse outcomes in patient welfare and safety. Ethical review must concern itself with the risk/benefit balance to the subject and to future patients of that type. Under the 2001 Clinical Trials Directive, specific matters to consider are the risk and inconvenience to the trial subject². It follows that the ethical review of a clinical trial requires a renewed assessment of the scientific merit of the study in order to determine whether the subject will be inconvenienced by the application of a badly designed or irrelevant protocol, and whether the scientific or social benefit of a weakly designed or statistically underpowered study is outweighed by the personal risk to the subject. Ethical review therefore cannot be conducted unless by reference to the safety and scientific merit of the protocol. This is because it is an inalienable legal duty upon the ethics committee to protect the rights, safety and wellbeing of the trial subject³. This legal duty means that any consideration of science or safety must at some point revert to the ethics committee, despite any prior allocation of that function to the competent authority. So any administrative attempt to separate scientific review from ethical review creates a dangerous tension with this prime requirement of the Directive. The question is not whether the components of ethical review can be split between different bodies. The question is whether the review of the ethics, the science and the safety of the protocol, and the grant of a clinical trial authorization, should be conducted by a new type of composite regulatory authority in the European member states. The following paragraphs argue the case for this.

² Clinical Trials Directive 2001/20/EC; Article 3, paragraph 2(a)

³ *ibid.*; Article 2(k)

How separation of governance functions cause systemic weakness

3. UK RECs are instructed that they need not make a separate review of the scientific quality of a protocol⁴, but that they need only be satisfied by credible assurances that the sponsor has taken account of appropriate scientific peer review. UK RECs have not been told what constitutes a credible assurance and I suggest that it is impossible to provide an effective definition. This creates a risk of inconsistent decision-making on the scientific aspect of the ethical review and this inconsistency could result in clinical risk to the trial subject. There is also some evidence that UK RECs do not feel comfortable in proceeding to ethical review without a consideration of the science⁵. They are right to require a review of the science as part of their ethical review.
4. A question therefore arises as to how ethics committees should best protect the safety and wellbeing of the subject. Should the Commission require the REC to make a separate consideration of the safety and scientific issues, in addition to that performed by the NCA, as a double safeguard to the trial subject? If so, then how can it be guaranteed that a REC system comprised of volunteers can generate a consistent level of expertise to ensure a consistent quality of scientific review across all RECs at all times? How can it be ensured that these separate reviews of the scientific merits of the protocol are not inconsistent with each other? Conversely, if the Commission maintains that the REC must be informed and guided by the scientific review carried out by the NCA, but that it is not the responsibility of the REC to conduct its own review, then it raises concerns about the degree of cooperation that does exist at present, and must in future exist, in the timely flow of information between the two institutions within the 60 day time limit imposed by the Directive for 'ordinary' clinical trials and the 90 day limit imposed for trials involving advanced therapies.

⁴ Governance Arrangements for Research Ethics Committees Proposed Harmonised Edition 2009 at paragraph 5.4.2 (a)

⁵ E L Angell, A Bryman, R E Ashcroft, et al. *An analysis of decision letters by RECs: the ethics/scientific quality boundary examined*. Qual. Saf. Health Care 2008 17: 131-136

The Ethics Committee as a Historical Relic

5. There is a separate problem concerning the quality and consistency of decision making in research governance. I suspect that one of the chief obstacles to consistency is the over-reliance that is placed at this time upon the *ad hoc* recruitment of volunteer members to ethics committees. Such volunteers may exhibit variable levels of skill, experience and applied training. Divergent, inconsistent or even erroneous decision-making can arise from these circumstances. The very structure of RECs as loosely affiliated committees encourages this to happen. In the United Kingdom, all National Health Service RECs are comprised of unpaid volunteers, some expert and some lay, and there is some evidence of substantial divergence in decision-making between these committees⁶. The problem is compounded by the requirement that the term of office of a UK NHS REC member is normally limited to 5 years, thus resulting in a loss of acquired experience and 'organisational memory'. I advance the proposition that whilst ethics committees were a necessary response to the circumstances prevailing in European clinical research in the decades after the Nuremberg Trials, and were adapted mainly to deal with research conducted within a University Hospital setting, they are not suitable for the governance of multi-national clinical trials taking place in an increasingly complex regulatory environment and at pan-European level. For example, the UK Department of Health has only recently acknowledged that it is the function of the REC to apply the law to the protocol under consideration and by implication to determine the lawfulness of the research⁷. Unlike ethics committees in some other member states, it is not a requirement of a UK REC that a lawyer be appointed to serve upon it. The scarcity of qualified lawyers serving on UK RECs, and the seeming lack of initiative by the UK National Research Ethics Service to recruit them, supports the proposition that UK RECs are not adequately equipped to deal with the legal and regulatory aspects of a research proposal. The difficulties that lay members might experience in correctly applying the law to the research protocol, and evaluating it against the legal rights and expectations of the trial subject, could also compound this inconsistency in decision-making between ethics committees. The deficiencies of the ethics

⁶ E Angell, A J Sutton, K Windridge, et al . *Consistency in decision making by research ethics committees: a controlled comparison* . J Med Ethics 2006 32: 662-664.

⁷ C.L.Roy-Toole. *The 'New Governance Arrangements for Research Ethics Committees': policy - shift and equivocation on matters of illegal research* . Research Ethics Review (2009) Vol 5, No 4, pp.160-161

committee may lie not only in the availability of their scientific expertise, but also in their applied legal knowledge.

6. It follows that the Commission should consider whether there is a compelling case for amending the Directive so as to expressly permit and to facilitate the institutional merger of the NCA and the REC into a single regulatory body in every member state. In this single body, the functions of scientific review and ethical review would be conducted by a single set of experts operating collaboratively and simultaneously to provide the ethical review and the clinical trials authorisation upon which commencement of the trial will depend. The new regulatory body for clinical trials would also supply its own opinion on the lawfulness of the research protocol and it would be staffed for this purpose. The question is whether this organisational structure should become the standard for all Member States. In the same way as the Commission is currently considering the allocation of functions between NCAs and the EMEA in the context of a single European Clinical Trials Authorisation, then similar considerations would have to be given to the relationship between these national regulatory bodies and a central regulatory body for clinical trials at European level. This 'super-regulator' would also combine the functions of ethics committee and competent authority so as to deliver a single ethical opinion and clinical trials authorisation at European level, where such an opinion would be required.

Expediting clinical trials authorization through a single point of submission

7. One can envisage that a prime reason for a REC to require further information from either the sponsor or the competent authority, and to delay the delivery of an ethical opinion, is the lack of independent scientific expertise available to the REC at the time that the application is submitted to it. Would it therefore become unnecessary to 'stop the clock', and to suspend the running of the 60 or 90 day time limit for clinical trials, if this new single regulatory body for clinical trials were possessed of a sufficient panel of experts to enable toxicology or immunology reports to be prepared in time and independently of any reliance upon the expert reports of the sponsor? Might the authorisation of clinical trials be expedited in this way? In the United Kingdom, arrangements are now in place to allow for the sharing of information between REC and NCA in the review of the scientific quality and safety of a protocol involving a clinical trial of an investigational medicinal product. In the case of high-risk and novel compounds, there is separate provision for access to an Expert

Advisory Group provided under the auspices of the NCA for the purposes of scientific and safety review. These arrangements were put in place in 2006 and were augmented⁸ as a result of the much publicized TGN1412 trial which resulted in grave injury to several healthy volunteers in a clinical trial unit attached to the Northwick Park Hospital in England. I am not aware of any study showing how well these arrangements are working in the transfer of information between the various bodies involved in the authorization or approval of clinical trials. Until there has been a thorough study of the efficiency of such an arrangement at European level, it cannot be said that the present separation of ethics committee from competent authority provides a system of comparable or superior efficiency to that which I now advocate.

8. By collapsing ethics committees and competent authorities into single regulatory bodies for the authorisation of clinical trials in member states, the Commission would reduce the number of permissions required for a clinical trial to proceed in a multi-national European setting, thereby reducing application costs. Deviation from 'normalized' decision making in the authorization process could perhaps be reduced as a consequence of having fewer bodies responsible for making those decisions. Local knowledge of local facilities is a prime advantage and so the establishment of a new regulatory body with regional application centres will very probably be required.
9. It should be remarked that a single regulatory body might also provide benefits for pharmacovigilance, in that it would remove the need for dual reporting of safety data to both competent authority and ethics committee. The ethics committee currently has a role to play in the pharmacovigilance requirements set out by the Directives. But the loosely affiliated ethics committee structures, meeting as they do on an occasional basis, are not naturally suited to the monitoring and supervision of pharmacovigilance data in clinical trials. Better then to collapse the pharmacovigilance role of the ethics committee into the supervisory role of a new regulatory body for clinical trials in each member state.
10. Would the cost of merger between REC and NCA be prohibitive? There is the question of how an expanded pool of scientific experts could be maintained at public expense. There is also the question as to how independent research ethics

⁸ MHRA/COREC/GTAC memorandum of understanding Final version 1 (dated 23 October 2006); *First time in man (FTIM) and other clinical trials subject to assessment by the Expert Advisory Group and Commission on Human Medicine*. A Letter from NRES to Chairs of RECs dated 14th August 2007

committees, customarily dealing with commercial Phase I trials, are to integrate into such a system. The creation of a single regulatory body is likely to require a greater reliance upon professionals under contract to work for it. But if the European member states desire harmonized research governance then they must be prepared to pay for it. If additional costs are incurred in implementing such a system, then those costs might be outweighed by the additional benefit to be gained from being able to run larger and better powered clinical trials across Europe, within a shorter time for commencement, and with better consistency in governance decisions. Such a system of regulatory bodies would be expected to facilitate, with sound ethics, the aims and objectives of the European Research Area vision whilst at the same time protecting the rights of the subject in research. Improved harmonisation by the use of coordinated regulatory bodies at European level might enable improved cooperation with governance systems outside the European Economic Area, so as to promote common ethical standards and governance systems in wider markets and to limit the occurrence of 'clinical trial dumping' in Developing Countries.

Functional inconsistency within the 2001 Directive itself

11. A regulatory body with dual functions is not contrary to main premise of the 2001 Clinical Trials Directive if the process of ethical and scientific review is seen in functional terms. By this I mean that the Directive attaches importance to the separate review of science and ethics, rather than a physical separation of ethics committee from competent authority. Such is the vagueness of the Directive on the matter of how functions are to be allocated between ethics committee and competent authority, that this interpretation may be the only way forward. Article 6(4) of the Directive permits the member state to direct that certain functions relating to the review of insurance and compensation, and normally carried out by the ethics committee, shall be performed instead by the competent authority. Article 3(2)(a) of the Directive states that the risk/benefit assessment needed for authorization of a clinical trial can be carried out by the ethics committee 'and/or' the competent authority. This provision blurs the boundaries as to what the respective roles of the two bodies are meant to be. It allows for the risk/benefit balance to be made by the competent authority, and so permits a separation of function on the matter of scientific quality and safety. But Article 3 provides no additional guidance as to how the ethics committee is to discharge its inalienable legal duty to protect the safety

and wellbeing of the trial subject , having remitted the duty to review the safety and the scientific issues to the competent authority . Conversely, the provision of Article 6(3)(b) infers that the ethics committee must then carry out a separate consideration of the justification for any risk/benefit assessment that has been made by the competent authority. This suggests a statutory requirement for a double review of the safety and scientific merits of the protocol in a way that would preclude this separation of function in the first instance . So the Directive is seemingly self-contradictory as to the ways in which functions can be allocated between ethics committee and competent authority in the ethical and scientific reviews of a clinical trial protocol. Any redefinition of the roles of ethics committee and competent authority would have to address these provisions of the Directive specifically. A better solution is to begin again and to permit all aspects of the review of a clinical trial protocol, leading to clinical trials authorization, to be conducted by a single institution. That single institution would need to have the characteristics of a regulatory body because that is what the competent authority is. The following paragraphs provide further reasons as to why it is necessary to merge the ethics committee with the competent authority in the grant of a clinical trial authorisation.

A new protection for Human Rights in Research Governance

12. If the reviewing functions specified in the Directive were to be allocated to the competent authority to the widest extent permitted by the Directive , then the remaining issues that would fall to an ethics committee to resolve would be those that engage the informed consent, informational privacy and other rights of the trial subject. These rights necessarily include the legal rights of the trial subject. It follows that the function of the ethics committee has , and has always had, regulatory overtones that concern the identification and protection of legal rights. It is possible that these issues have never been adequately or fully acknowledged in the working out of the Directive. This is certainly true of the United Kingdom⁹. In the United Kingdom at this time, and perhaps in other member states besides, there is no regulatory body that has the express responsibility for protecting the legal rights of the research subject in a clinical trial *at or before the point at which they become involved in the research*. This is a signal failing in the UK research governance

⁹ C.L.Roy-Toole. *Illegality in the research protocol: the duty of research ethics committees under the 2001 Clinical Trials Directive* , Research Ethics Review (2008) Vol . 4, No 3, 111–116

system. It is a signal failing of any other governance system that operates in the same way. The new model for regulatory bodies will remedy this. They will apply legal rights protection in addition to that offered by the public courts at or before the point at which the subject begins to participate in the research. Public confidence in research might improve as a consequence and this might benefit recruitment to research. A single regulatory body for the clinical trials sector, embracing the functions of competent authority and ethics committee, could thereby enable the legal rights dimension of clinical trials authorization to be developed in a new and dynamic way. These new regulatory bodies could become an interface between law and science and could assist in the development of a responsive and reflexive body of legal protections for humans in clinical research at European and national level.

13. The circumstances of the TGN1412 trial at the Northwick Park Hospital in the United Kingdom were such that the injured volunteers were allegedly left without adequate insurance cover and yet the protocol had been approved by a NHS REC. The circumstances of this episode should be re-examined to determine whether additional lessons need to be learnt as to how the legality of research should be evaluated and policed in any research governance system. I might add that I prefer the use of the term 'research 'subject', rather than 'research participant', as some have suggested, because the patient in clinical trials research is often incapacitated or vulnerable, and potentially at substantial disadvantage in his involvement. The use of the word 'subject' conveys this fact plainly and without pretence to those who have the responsibility to protect them.

Independence in Research Governance

14. The only apparent reservation against wholesale merger and absorption of the ethics committee into a single regulatory body is contained within the definitional provision in Article 2(k) of the Directive. It stipulates that the ethics committee must be an 'independent body' within the member state. I interpret this requirement to mean that the ethics committee must be independent of the executive arm of the government and independent of the sponsor or researcher. Independence could still be retained if a separate regulatory body were to be established in the member states with powers that were sufficiently distinct from that of the executive arm of the state. To ensure its independence, it would need to operate under enabling legislation that would define its role and its powers and the apparatus for its own oversight and

scrutiny. An appeal structure would be needed from the decisions of this regulatory body at first instance and this would be an institutional appeals structure of some kind. The ultimate sanction for any public authority is through the public courts. A problem with regulatory bodies is that they become static and sometimes unwilling to adapt their own practices or to make full use of their powers. The fewer the decision makers, the more stagnant the decision making process will become. So there must be a responsive and reflexive system of scientific and ethical advisory boards appointed to advise and to oversee these new regulatory bodies, so as to ensure that they respond to changes in good clinical practice and to social needs. The need for a specific regulator for other forms of clinical research not involving Investigational Medicinal Products [IMP] would also have to be considered. Is it more efficient to separate the regulatory bodies according to the type of research in question or to have a general regulator for all bio-medical research? This question must be addressed. But there are financial and logistical issues involved in this exercise that are beyond my current capacity to address.

The case for a New Framework of Legal Rights for Humans in Bio-Medical Research

15. The case for new regulatory bodies for clinical research should be considered alongside the case for a new European framework for the legal rights of the subject in bio-medical research. These are separate questions to that of a new and all-embracing Directive for the authorization and conduct of clinical research not involving IMPs, as is mentioned in the present consultation. But the issues are linked. Might this new legislative framework for legal rights do more than anything else to promote harmonization in European research governance for clinical trials? Insurance, indemnity, compensation for negligent and non-negligent injury, data protection, privacy and valid consent to inclusion in research are the main issues that would inform this new legislative framework. These are the matters upon which the laws of the member states are divergent. Relevant here is the question of the absolute rights and the qualified rights of the individual as expressed through the European Convention on Human Rights. The latter can be mediated by recourse to the powers of the state and the wider public interest. It follows that this new framework would need to specify the legal rights of the research subject by reference to the Convention and specify how the regulatory body and the courts would protect

these rights. But it would also need to set out how regulators and the courts would mediate those personal rights against the wider interests of society in the benefits of research.

Research Governance and Information Governance are linked

16. Data Protection for research participants is a major issue in this. There is a specific question that has yet to be resolved as to whether UK Data Protection laws are fully compatible with the European Data Directive. It is doubted whether UK laws are sufficiently stringent in their requirements for the anonymisation of personal data in order for this exemption to apply. Some European countries, especially Germany, demand more stringent standards as to what constitutes non-identifiable personal data. Resolution of this matter will impact upon the ease with which epidemiological database research can be carried out in a multi-national European setting.
17. It should be noted that there is a parallel European Commission consultation on the future of the Data Directive that is almost synchronous with the present consultation on the future of the Clinical Trials Directive¹⁰. I ask that my submissions on the reform of information governance in bio-medical research be considered under both consultations. In addition to any reform of the Data Directive in matters of general or commercial data use, there is a strong case for examining the specific usage of bio-medical data and research data, not only within the ambit of the present consultations, but also as a separate topic for future consultation in its own right.

New Information Laws for a new Society

18. In this regard, there is a specific problem in clarifying the scope of the exemption under the European Data Directive¹¹ for the use of personal data in research. These issues have been considered already as part of the EU Framework 5 PRIVIREAL project. I do not share the confidence of the PRIVIREAL group when they assert that no further amendment of the Data Directive is required in this matter of the exemption for research¹². There is the problem of the Data Directive's in-built redundancy when faced by future technological advancement and the resulting

¹⁰ http://ec.europa.eu/justice_home/news/consulting_public/news_consulting_0003_en.htm

¹¹ Directive 95/46/EC, Articles 13(2) and 32(3)

¹² <http://www.privireal.org/content/recommendations/#Recd>

changes in modes of data usage in this time of 'ambient' or 'ubiquitous' computing. Already the UK Information Commissioner has recommended additional safeguards in the form of Privacy Impact Assessments to inform new and complex applications involving the use of personal data¹³. This indicates that the UK Data Protection Act 1998 is not sufficient to deal with the modern informational environment without supplementary evaluation tools. A recent survey conducted by RAND at the behest of the Information Commissioner in the United Kingdom concludes that the Data Directive is outdated and overly bureaucratic and cannot suffice in the long term¹⁴. I adopt many of the RAND recommendations in my own submissions. There are other problems with information governance in UK bio-medical research that could be resolved, or at least assisted, by legislative intervention at European level. These are discussed below. For these reasons, I contend that a new European legislative platform is necessary for the use of personal information in bio-medical research in a multi-national setting.

Systemic problems in Health Information Governance in the United Kingdom

19. A specific problem for information usage in UK bio-medical research lies in the fact that there are two separate legal restraints that govern the use of patient information in this country. The first is the Data Protection Act 1998 and the second is the common law duty not to misuse private information. These legal systems appear to run in parallel but they can give rise to divergent results. Personal data can be exempted from the Data Protection Act if it is non-identifiable but it can also be used if it falls within a permissible ground or a defined exemption. At common law, private information can be used by consent or by recourse to an appeal to the public interest or to a competing legal right or a legal compulsion. Anonymisation is not necessarily a permissible ground to use private information without the subject's consent, although it seems that current NHS policy may treat it as such. All this is an anomaly in the UK clinical research context, because it has resulted in a situation in which there are separate regulatory bodies with seemingly overlapping responsibilities for the governance of personal information in research. Data protection issues in

¹³ http://www.ico.gov.uk/upload/documents/pia_handbook_html_v2/html/part1.html

¹⁴

http://www.ico.gov.uk/upload/documents/library/data_protection/detailed_specialist_guides/review_of_eu_dp_directive_summary.pdf

medical care are ultimately governed by recourse to the Information Commissioner , a body that is not geared specifically to the clinical research sector , and is outside the National Health Service . Issues relating specifically to the non-consensual use of private information in database research are dealt with by an arm of the new NHS National Information Governance Board for Health [NIGB], by means of general or special permissions that render the information usage lawful notwithstanding any legal duty of confidentiality¹⁵. Processing patient information through cancer registries is one example of this permission¹⁶, as is the approval of a single and time-limited database project to be conducted without patient consent . Because of vague statutory drafting, it is unclear whether such permissions exempt the data from the requirements of the Data Protection Act as well¹⁷. As a matter of jurisprudence, they should not. NIGB has no regulatory function under the Data Protection Act and is only an advisory board to the Secretary of State in such matters . But researchers and NHS staff might have a different impression.

20. A recent survey in the United Kingdom has indicated that public opinion is mixed as to the circumstances in which researchers should be able to access personal data for additional research uses¹⁸ without the consent of the subject . But the surveyed responses incline clearly towards the requirement for consent in the use of identifiable data. The UK Academy of Medical Sciences has elsewhere suggested that more emphasis should be placed upon the public interest to justify non-consensual information usage in research, together with the current research exemption under Section 33 Data Protection Act 1998, in preference to what it sees as a preoccupation by current NHS regulators with a requirement for consent or anonymisation¹⁹. The Academy also proposed an enhanced role for ethics committees in that their approval of non-consensual research uses should also serve as a defence to legal claims made against the researcher . However, the lack of legally qualified members serving with UK research ethics committees and the inconsistency of their decision-making make this proposal problematic.

¹⁵ National Health Service Act 2006, section 251(2) (c)

¹⁶ The Health Service (Control of Patient Information) Regulations 2002

¹⁷ National Health Service Act 2006, section 251 (7) and (8)

¹⁸ http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_109343.pdf

¹⁹ Academy of Medical Sciences Report: *Personal data for public good: using health information in medical research*, January 2006

Reform of Information Governance in UK Bio -medical Research

21. It follows that clinical research in the United Kingdom would operate more efficiently if there was to be a new and specific legal framework for information usage in all forms of bio-medical research that abolishes the parallel system of regulation that currently prevails and establishes a new classification of information rights for the research subject supported by an adaptive privacy test. This could mean the application of a risk-based approach to information governance in preference to a process-oriented approach seen under current national laws. A specific issue here is that whilst new and permissive regulatory approaches could be taken to information usage in commerce and general society, the privacy risks inherent in research may mean that a more prescriptive and interventional approach could still be required in order to regulate the bio-medical research sector. Solutions that might apply in business might be inappropriate to research. The recommendations of the RAND report need to be read in this light²⁰. But the general approach to research regulation would still need to be flexible in order to respond to a rapid development in technological and methodological bases for research. Privacy concepts would therefore need to be worked out and defined in law so that risk assessments could be made and harmonized principles encouraged with other member states. A formulation of General Principles and Desired Outcomes, as discussed in paragraph 26, would be relevant to this. This new framework would obviously need to examine when and how personal information can be used in a research context, with or without the need for express or implied consent, and to determine how and when the subject should continue to have control over that information, or at the very least be informed that the use of personal information is taking place. The circumstances in which statutory permissions would be needed, or standing exemptions allowed, would have to be thought out afresh. The Section 33 research exemption should be reframed or replaced under UK law for the sake of clarity, and the corresponding provision in the Data Directive needs to be reviewed in the interests of modernity. The new system should also rely upon different compliance tools that could be more specifically targeted to areas of risk that will change over time, rather than seeking a 'one-off' or 'one-size fits all' solution to information governance. This might allow

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http://www.ico.gov.uk/upload/documents/library/data_protection/detailed_specialist_guides/review_of_eu_dp_directive.pdf

researchers the chance to regulate themselves to some extent, by selecting the right tools, rather than relying upon data protection authorities to do it for them with requirements that might be seen as overly burdensome or bureaucratic. Some of the other issues that might inform the debate on new approaches to information governance in bio-medical research are discussed in paragraphs 26 to 28 below.

22. The need for a separate legal code for information governance in bio-medical research can be justified on the reasoning that it is in the use of health information that the tension between the private interests of the subject and the wider interests of society are most keenly, and dynamically, expressed. The basic legal provisions also need to be capable of being easily understood by medical workers as well as lawyers and at present this is not the case²¹. If these reforms are needed in the United Kingdom, then they are likely to be needed in other member states besides. A comparative translational legal study should therefore be made as to how such a new approach to information governance would impact upon bio-medical research sectors in member states.

A new regulatory body for Health Database Research

23. There arises the separate question as to whether there should be a new and specific regulatory body for information governance in bio-medical research. I consider that such a body is necessary. Insofar as the approval of an ethics committee is currently required for certain types of database research²², then those functions currently performed by the ethics committee could be merged into that of a new regulatory body for information governance in bio-medical research within each member state. This should certainly be done in the United Kingdom. There is at present an agreement between UK RECs and the relevant arm of NIGB to share information in the approval of database research. The most important decisions are made by NIGB because it has the power to override the common law duty of confidentiality. So there is a question as to whether the need for additional consideration by a REC is a formality that is becoming increasingly unnecessary. Only the disjointed nature of information law in this country preserves the need for the REC in the approval of database research. This approval process might be more easily accomplished by a

²¹ PRIVIREAL commentary on the research exemption under Section 33 DPA 1998

²² For an example from the UK, see The Health Service (Control of Patient Information) Regulations 2002, regulation 5

single regulator operating under a comprehensive legal framework and staffed by persons capable of providing ethical critique. Approval time might be speeded up and the number of separate permissions reduced accordingly. A relevant counterpoint is that the volume of research applications to the new regulator would be much greater than that currently handled by NIGB, because the latter's case-load is necessarily confined to research applications involving non-consensual information usage at this time. Scientific and ethical advisory boards, appeal structures and public accountability would also be required in a way similar to that required by any regulatory body for the clinical trials sector. Translation of this proposal into the framework of national laws within each member state will be the major issue. A comparative legal study of the feasibility of this proposal will therefore be necessary. A separate question is the legal and functional relationship that would exist between this new regulator for information governance in bio-medical research and the supervisory authority required in every member state under the terms of the Data Directive. Does the one need to be answerable to the other? Should the Data Directive be amended so as to better reflect the need for new sector-specific regulators for information usage in member states? The single regulator for research information governance would then be expected to implement the new rights framework for bio-medical research, when it is devised.

A new legal framework for European collaboration in Health Database Research

24. One potential application for a new information governance framework for bio-medical research, and the new regulatory bodies that would implement it, is to assist in the establishment of pan-European registries for disease surveillance designated as important to public health. The protection of Cancer Registries is a pressing example of this. The UK Ministry of Justice Data Sharing Review of July 2008²³ noted that the UK Data Protection Act was not optimized for easy application. It acknowledged that there was a need for 'fast-track' legislation to promote data sharing arrangements that could show a clear need, and that such legislation could be used to establish 'Safe Havens' for research and statistical applications. These safe havens could specifically address the problem of accessing patient information for research where no research consent has been obtained beforehand. The present

²³ <http://www.justice.gov.uk/reviews/docs/data-sharing-review-report.pdf>

need for some form of prior consent is a relevant factor even in the operation of the Section 33 research exemption when measured against the 'fair processing' requirements of the 1998 Act. A robust 'public interest' test would be required to facilitate such data usage without consent. But it would be necessary to temper this power with the need for adequate privacy safeguards or else the public would be unlikely to accept it. The availability of a right of review and the limits of judicial challenge would also be important in this respect. One might expect that safe havens would enjoy exemption from the burden and expense of normal data processing rules relating to consent, and subject information or access provisions, on condition that adequate data security could be demonstrated by periodic audit. This would have to be coupled with arrangements for the controlled release of data to other research applicants, in which the privacy rights of the subjects were to be adequately protected. In other classes of database research deemed to be a lesser public priority, regulatory consensus about a subject's right of 'opt-in' or 'opt-out' could mitigate concerns about privacy violation in research. The impetus and guidance for this new framework should come from the European Commission at first instance. It demonstrates that there is a need for harmonisation in the application of information laws across member states so as to facilitate multi-national research in epidemiology and allied fields.

25. Would national data protection laws impede the establishment of a 'super-regulator' for information governance in research at central European level and thus impede the grant of a single regulatory permission for European-wide epidemiological research? If so, then systematic reform and clarification of the Data Directive is required in order to improve harmonisation. This is discussed below.

The Reform of the Data Directive and the application to Bio-Medical Research

A Risk-Based Approach to Privacy Protection

26. The RAND report concludes that the Data Directive must be re-worked so as to provide clearly understood 'General Principles' and 'Desired Outcomes' that can then be adopted and applied by member states. RAND acknowledges that the current Data Protection Principles can still be used as a basis for this. It is not suggested that the principles in the Data Directive be abandoned. But RAND also recommends that the Data Directive should not be the place to make prescriptive process-oriented statements about how data protection should be implemented in member states. Instead, having grasped and affirmed the general principles, the member states would be left to select their own compliance measures based on a local assessment of areas of privacy risk. The adequacy of current legal protections under national laws in member states would presumably be a decisional factor in this. The users of personal information would therefore have greater responsibility to ensure self-compliance with those general principles and would do so using a range of privacy tools that should be developed and applied according to circumstance. If there was a breach of the general principles, or a deviance from the desired outcomes, then harsher penalties could follow based on a risk assessment of where enforcement is most needed. So compliance with data protection principles would be achieved, as it were, by following the 'spirit of the law' rather than static procedural forms that have no relevance to the risk. This means that in general and commercial data processing there would be less reliance on the requirement of notification to the data protection authority and greater emphasis upon individual risk assessment and self-policing by the users of that data. Health information is acknowledged by RAND as an area of special privacy risk. But it must be remembered that the RAND report does not deal specifically or in any detail with information governance in bio-medical research. So readers must decide whether recommendations in the report are inapplicable to the present consultation or else adapt the material that is considered to be relevant to the reform of information governance in the bio-medical research sector.

Adaptive Privacy Tools for the Bio-Medical Research Sector

27. If one were to apply the recommendations of the RAND report to both of these current European Commission consultations, then users of research data might be encouraged to adopt any number of a range of privacy tools to suit the circumstances of the research and commensurately with the privacy risk reflected by that research. Privacy Enhancing Technologies built into research methods are potentially one of the tools that might influence the assessment of the risk to privacy posed by the research project. A Privacy Impact Assessment will also help in deciding which tool to select. Other tools might include the use of research sector-specific Codes for Information Governance issued by the regulator, which would require voluntary acceptance by the user but also an explanation as to why they were not followed, together with agreed Standards for information usage in research based on the European or British Standards, and information compliance Kite-Marks for research networks so that competition in compliance quality could be encouraged. Codes of Conduct devised by researchers themselves could also be developed and approved. In order to promote better relationships of trust and understanding with the research subjects. Privacy Notices, adapted for relevance and ease of comprehension, could be used as an advance indication of research information usage and could then be referenced or supplemented in the patient information literature that is required as part of the informed consent process or the application process for research approval. Common standards in the research sector would help to take the 'mystery' out of seeking regulatory approval for research and might also reduce the number of amendments to the protocol that are currently needed. The level of understanding of data protection issues by some researchers in the United Kingdom is still highly variable to the point of error, and I base this remark upon my personal experience. Better self-education within the research community is definitely needed. Instead of being left to the lawyers, information governance must be instilled reflexively in researchers themselves. An intelligible and updated legal framework will enable them to do this.

A new Legal Architecture for 'Globalised' Research

28. The RAND report is especially critical of the current implementation of the Data Directive in the export of data to non-European countries in this 'era of globalisation'. The 'adequacy' test is seen as outmoded in deciding whether data controllers in one country should be allowed less onerous compliance requirements in data protection matters than others, and especially since some non-European countries might have data protection rules that equal or exceed those of the member states. The operation of the Health Insurance Portability and Accountability Act in the United States is cited as an example of that. The adequacy test also overlooks the most important question, which is whether the data controller is actually protecting the rights of the subject and whether it can be made accountable for it. The current approach to trans-border data flows is seen as a major obstacle to commerce. I pose the question that it might also be an obstacle to international research cooperation. RAND favours alternative solutions for commercial data processing in the use of Standard Contractual Clauses [SCC] and Binding Corporate Rules [BCR]. It is considered that more work is needed to harmonise the use of SCC across member states. The use of BCR is also problematical. It allows BCR to be accepted on a mutual basis by data protection authorities in different member states, but approval takes longer for the same reason. These solutions are far from perfect and might only be a temporary solution pending a wider reform of the Directive. However, these solutions are also relevant to the harmonisation of bio-medical and clinical trials research across European member states. By adopting a translational approach, these solutions could perhaps be adapted to deal with other legal issues in research governance besides data protection. The following paragraphs explore this point.

Using Legal Contracts to facilitate Harmonised Research

29. In the event that harmonisation of legal principles should prove impossible between the member states, in the short to medium term, by the reform of the Clinical Trials Directive and other applicable Directives including the Data Directive, then an alternative solution should be evaluated in the specific context of clinical research. This alternative solution could involve the use of model and adaptive contracts between sponsors, research institutions and contract research organizations, in the various member states or outside them, by which the legal rights of the subject and the legal rights of the researchers could be defined and protected in the course of the

research process and after it. The OECD has already pioneered the use of model contracts to ensure compliance with the European Data Directive in cases involving trans-border data flow outside the European Economic Area [EEA]. Might the OECD be encouraged to develop similar model contracts for the promulgation of multinational clinical trials not only inside, but outside, the EEA? It might be open to contracting participants to agree a choice of laws to govern their arrangements. If laws relating to insurance and compensation provisions in the relevant member states are divergent, then the contract might specify a free-standing insurance and compensation arrangement to be applied across member states to the benefit of the research subjects in the study. It would then be a legal and ethical issue for the regulatory body for clinical trials to determine whether this insurance and compensation arrangement is fair when compared to the arrangements that would normally apply to the research subjects in their own countries. Similar arrangements could be devised for issues relating to data protection and informational privacy in a clinical trial setting. Would this allow a harmonized approach to legal issues that could be constructed within the ambit of a single study, or linked studies, through the mechanism of contract? Or would divergence in national laws and legal remedies give rise to insuperable legal and ethical problems?

30. If this contractual solution were to be adopted, then the regulatory body would be required to vet the use of model contracts and any adapted contracts. Would it be necessary for the regulatory body to vet such contracts in every multi-national research study taking place within a member state because of the special risks to the human subject inherent in research? The answer to that question is probably yes. This differentiates the use of model contracts in research from the use of adapted standard contractual clauses in commercial data exports where no such regulatory approval is required. Skills in Comparative Law would be needed, no matter what the answer to that question. It follows that this new regulatory body for clinical trials would have a clear legal function in that it would deal directly and expressly with the legal rights of the participants and would give effect to those legal rights by modalities that could be statute-based and also contract-based. Should these contractual arrangements, if approved by a regulatory body in one member state, become legally binding in other member states and without the need for separate approval? One might assume that contracts should be self-governing no matter where they are concluded, but the special risk to the subject in research renders the

question of reciprocal acceptance problematic and more stringent approaches may be required to the problem. I do not know how far this solution of the model contract has been explored by the research community in the multi-national context. Material Transfer Arrangements relating to the use of human tissue have been a feature of clinical research for some time. It is a matter that should be studied specifically by the Commission.

31. In the case of established research networks operating at a pan-European level, and especially those dealing primarily with database research, consideration should be given to whether data protection compliance can be ensured, and the process of research approval facilitated, by the use of a device comparable to the current arrangements for Binding Corporate Rules. This would need to be examined against the current requirement to obtain express consent of the subject for data transfer outside the EEA in cases where no alternative solution is provided. If the data protection arrangements of a research network are approved in this way, then it would allow a kind of limited 'research passport' for researchers to collaborate in member states that acknowledge those Rules on a mutual basis, and so too with third party collaborators outside the EEA. Might this arrangement assist the development of larger pan-European networks for research and so assist in promoting the European Research Area strategy amongst non-European partners? The legal rights and responsibilities covered by these BCR arrangements for research would chiefly relate to data protection and informational privacy. But could arrangements similar to BCR be extended in law to cover other types of rights? A new legislative framework would be required for that purpose.

Harmonisation of Insurance and Indemnity Arrangements in Research

32. Consulted organisations have already made recommendations as to how insurance and compensation arrangements for research subjects can be improved in multi-national research across European member states. I urge the Commission to give active consideration to these recommendations. ICREL has recommended the development of 'block' packages for insurance in clinical research as an alternative to the insurance of individual studies²⁴. Such block insurance arrangements might be shaped by comparison with those for public health systems and associations of

²⁴ ICREL Final Report: *Impact on Clinical Research of European Legislation*, 2009

commercial pharmaceutical manufacturers. ICREL recommends a major taskforce be set up to consider the feasibility and implementation of such arrangements. The European Science Foundation has made similar recommendations ²⁵.

A Risk-Based Approach to Insurance

33. A relevant issue is the risk assessment for the purposes of fixing the cost of insurance when it is purchased on a 'block' basis. If a single study is insured, then the risk assessment should be clear. The level of cover will be fixed by reference to the possible level of compensation to be awarded or other loss to be covered. But where block insurance is purchased for multiple studies, the insurer's risk assessment becomes less certain. The insurer's response to this might be to inflate the cost of cover so as to protect against hidden risk. A second issue is the cost of renewal of this block insurance package in the event that a claim is made against a single subscriber who forms part of a group of subscribers. What is the added cost to the group caused by the resulting increased default risk that they now represent? Would this lead to adverse consequences as defaulting research organisations with a claims history are marginalised by other organisations with none, in the interests of preserving low insurance costs? Another consequence of following the block purchasing model is that insurance might be grouped not according to research topicality but according to clinical risk. Insurers might be more amenable to block insurance arrangements where they concern studies with a broadly similar risk profile in the potential harm to the research subject. This could mean that insurance might be more readily provided if it fell within a type of clinical research practice with an ascertainable risk profile, as opposed to research that is broadly assessed as falling within a particular disease topic. Thus it might be more practicable for research organisations from different topical networks to secure block insurance arrangements if their research were to be assessed as falling within a category of assumed low risk, such as a comparative study of drugs within their marketing authorisation and with patients with characteristics covered by the indication specified in that authorisation. Studies of intermediate risk might require payments from a larger body of subscribers in order to keep costs down. The adverse consequence of this might be that orphan studies or very high risk studies could be marginalised in the insurance market. Subsidies from the mainstream research

²⁵ ESF: *Investigator Driven Clinical Trials*

community could perhaps fund the cost of these smaller but costlier studies . Alternatively, they might need to seek the assistance of the commercial research sector in a private-public partnership. I should remark that I am not an expert in insurance or reinsurance and these observations are hypothetical but not evidence-based. However, I suspect that they might prove to be prescient.

Contractual Compensation Schemes as an ethical tool

34. From such block insurance arrangements, might it be possible to construct free-standing compensation schemes for the benefit of the research subject that might operate autonomously, or at least semi-autonomously, to the compensation arrangements established under national laws of member states? This is relevant to the question no-fault compensation schemes that do not depend upon prior proof of negligence by the researcher in the harm caused to the subject. Such no-fault schemes are recommended by the Association of the British Pharmaceutical Industry [ABPI] and they are often found in commercially sponsored clinical trials in the United Kingdom, but never, in my experience, in trials sponsored by the UK National Health Service. No-fault schemes in the United Kingdom are not a substitute to negligence claims against fully insured defendants because the former is applied on a discretionary basis according to the severity of harm suffered. These no-fault schemes differ according to whether the claimant is a healthy volunteer in a Phase I study or a patient with underlying health problems under treatment in a Phase II or III study. There is also some doubt as to whether compensation schemes on the ABPI model are intended to be enforced as binding contracts in Phase II or III studies. This is because the guidance recommends that they be made ‘without legal commitment’²⁶. These schemes should be treated as contractually binding no matter what sort of research study is involved. The provision of no-fault compensation is unlikely to cure the divergence between the national laws of member states in the provision for compensation for harm suffered in the course of research. However, in multi-national trials, where there is a disparity in the level of protection offered by member states, no-fault compensation might do something to ‘level the playing field’ in the legal protections that the subjects are offered. Consideration should be given to the ethical issues raised by such a scheme. Would it savour of an inducement to

²⁶ C.L.Roy-Toole. *Illegality in the research protocol: the duty of research ethics committees under the 2001 Clinical Trials Directive*, Research Ethics Review (2008) Vol . 4, No 3, 111–116

enter research for poorer people who would not usually receive such protection in health care, or should it assist the ethical approval of multi-national studies that adopt such a scheme?

35. If block insurance could also provide an independent compensation scheme for negligent harm in multi-national research studies, and in accordance with a level of protection afforded to those research subjects who enjoy the most generous protection according to their own national laws, then that would obviously be the 'magic bullet' for European research governance. It would require a European consensus as to acceptable levels of insurance cover to be provided and the circumstances in which it should be applied. I am not confident about the prospects of achieving this, but it must be explored. If this could be achieved then it could perhaps be implemented by recourse to the legal contractual methods that I have described above, as a speedier alternative to a new legislative platform based on a Directive or a Regulation. It must therefore be investigated whether such compensation schemes can be reciprocally enforced throughout the European member states, and in any other state in which the research is likely to be carried on, through the mechanism of a legal contract.

Risk-Based Pharmacovigilance and Specific Modalities in Clinical Trials

36. A major issue raised in this consultation is whether the Clinical Trials Directive fails to differentiate the governance requirements of clinical trials conducted by commercial sponsors proceeding towards marketing authorisation from the practical requirements of publicly funded research using medicinal products that are already authorised or partly authorised for use in human subjects. A separate issue is whether legislative reform is needed to redefine the nature of a clinical trial or of an IMP to remove ambiguity as to what is an interventional or non-interventional trial, and so to clarify when the Directive should apply, but also to acknowledge the diversity of methods in academic clinical research beyond a rigid 'Phase' classification. A further question is whether a new legislative approach is needed to re-classify all types of clinical research and provide a harmonised governance framework that can be applied across all member states. At the centre of these proposals is the notion of replacing prescriptive forms and inflexible classifications with a new form of assessment that measures the required governance action according to the risk. We

have seen a similar approach recommended in the reform of the Data Directive. I therefore endorse the need for an enquiry into the value of risk-based assessment in clinical trials authorisation and pharmacovigilance. However I advise caution and issue warnings about some of the recommendations that have been advanced by some of the contributing organisations.

Multiple Sponsors and the 2001 Directive

37. To evaluate the strength of the case for risk based assessment, it is first necessary to deal with some questionable assumptions revealed by other respondents and by the authors of the present consultation. Firstly, it is wrong to state that the Directive does not permit co-sponsorship or multiple sponsors. The Directive never contained such a prohibition. References to the sponsor in the singular should include the plural form. This is how UK law has approached the issue²⁷. The European Commission has issued guidance in its *Questions and Answers on Clinical Trials* dated 28th July 2009 which specifically allow for an organisational grouping of researchers to become, in effect, multiple sponsors. Sponsors can also delegate their responsibility to agents, whilst still retaining legal responsibility for the duties of the sponsor.

Defining the Specific Modalities for Non-Commercial Trials

38. There is also the question of the special arrangements, or 'specific modalities', that can be afforded to non-commercial clinical trials under the 2001 Directive and 2005 Directive. Specific modalities need to be understood before we can begin to decide whether they should be supplemented, or even replaced, by a risk based governance assessment. Specific modalities can be applied to non-commercial trials involving investigational medicinal products used within their marketing authorisation and involving patients with the same characteristics as those covered by the indication specified in the authorisation. Non-commercial trials are defined as those conducted by researchers without the participation of the pharmaceutical industries. Recital 14 of the 2001 Directive refers to this limited category of research and labelling is the specific modality that is referenced there. But Recital 11 of the 2005 Directive also allows for the extension of specific modalities to apply to non-

²⁷ <http://www.ct-toolkit.ac.uk/db/documents/sponsorship.pdf>

commercial trials outside the terms of the marketing authorisation and for new indications. The specific modalities referenced there are, *in particular*, the relaxation of the manufacturing and import requirements for authorisation and of the submission and archiving requirements for the trial master file. This would tend to suggest that Recital 11 permits other modalities to be devised that fall outside these types. Article 1(4) of the 2005 Directive affirms the special position of trials of medicinal products within the terms of the marketing authorisation, but Article 1(3) also permits member states to devise other specific modalities for other academic clinical trials outside that marketing authorisation. Article 1(3) appears to limit the specific modalities that may be devised to those of a type referenced in Chapters 3 and 4 of the Directive, and which concern manufacturing, import and documentation. The Directive does permit member states to make their own rules as to specific modalities, provided that they are compatible with the Directives and the associated guidance. It is therefore unclear whether specific modalities that are not of these types are permissible under the Directives.

Is there a better alternative to Specific Modalities?

39. So a first question is whether member states have already done all that they can to extract the maximum benefit from the tolerances allowed by the specific modalities as they are currently defined. The second question is whether a risk based approach to research governance would allow other tolerances to academic clinical trial research and which go beyond those contemplated in the specific modalities. In answer to this second question, it would appear that the specific modalities are limited to labelling, manufacturing, importation and documentation. The specific modalities do not exhibit characteristics obviously associated with, and reflecting the results of, an assessment of risk arising in the context of individual studies. For the most part, they merely reflect the fact that regulatory requirements for trials of authorised drugs can often be achieved by reliance upon other work done in the authorisation phase. The obvious application of the risk based assessment is in the matter of pharmacovigilance. The 2001 Directive sets out the requirements for pharmacovigilance separately to those of the specific modalities. From this we may surmise that the optimisation of specific modalities would not provide additional tolerances to academic researchers in the extent of the pharmacovigilance required for academic trials involving marketed drugs that are to be tested inside or outside

the terms of their marketing authorisation. But it should be noted that ECRIN recommends that specific modalities be extended to all bio-medical research and also to research involving public-private partnerships²⁸. So it may be that specific modalities have continued usefulness in wider research, but it is uncertain whether they can be extended into new types of modality which are different to those currently referenced by the two Directives.

A Risk-Based Approach to Safety Monitoring

40. It follows that it is necessary to make an evaluation of risk based assessment in research governance under the Clinical Trials Directive, but only if one question can be answered in the affirmative. It must be shown that the pharmacovigilance requirements of the Directive can legitimately be modified to reflect the different research methods that are typically adopted in academic clinical trials of medicinal products. If pharmacovigilance requirements cannot be modified to reflect a difference in method between clinical trials of new drugs and trials of drugs within established terms of use, then it is hard to see what benefit there could be in pursuing a risk based assessment approach to research governance. What would researchers otherwise hope to achieve by it? It is surely accepted that pharmacovigilance includes the notification of safety-critical adverse events to the sponsor and the notification of serious adverse reactions to the competent authority, as specified by the 2001 Directive. So the specific question is how and in what circumstances might a risk based approach to pharmacovigilance enable the researcher to modify the requirements relating to adverse event reporting to the sponsor? A subordinate question is whether such an approach can be adopted already without any substantial reworking of the Directives.

²⁸ http://www.ecrin.org/index.php?option=com_docman&task=doc_details&gid=42&Itemid=68

Risk-Based Pharmacovigilance in the United Kingdom

41. A guidance document already exists which uses a risk based assessment approach to pharmacovigilance. It was issued by the Department of Health/Medical Research Council Joint Project in the United Kingdom in January 2007²⁹. It should form the basis of special scrutiny by the Commission and the stakeholders in this consultation to see whether similar approaches have been adopted, or can be adopted, in other member states and with a view to harmonisation. This guidance acknowledges that there can be different risks associated with the conduct of the trial of a new drug when compared to the trial of authorised drugs inside and outside the scope of the marketing authorisation. The level of risk may be reflected in the outcome measures adopted by the study. Not every adverse event might be relevant to the outcome measures of the study. The nature and frequency of adverse event reporting by the researcher to the sponsor will be determined by a risk assessment that determines which adverse events are relevant. It is open to the sponsor and the researcher to agree what types of adverse event will be reported or not and say why. This approach should reduce the burden of unnecessary data reporting. One factor that might have a bearing on whether a serious adverse event is reported is whether it has a causal relationship with the drug under test. So the quality of the scientific design of the study is very important in enabling the competent authority to assess the validity of the risk/benefit assessment that has been made and the pharmacovigilance method that has been adopted. The use of Data Monitoring Committees and the use of on-site or centralised data monitoring to support decisions on the relevance of adverse events are further issues for the researcher to consider. So it can be said that a risk based approach to pharmacovigilance will enable researchers to conduct trials of established drugs in a less burdensome way than for a trial of a drug used for the first time in humans. There will be other types of study falling in between these two examples that will necessitate varying but risk-adapted arrangements for safety reporting. The national guidance is not prescriptive. The question is how far the research community has travelled in arriving at a consensus as to what sort of monitoring arrangements are appropriate to the risk occasioned by the specific circumstances of the study to be undertaken. That is a

²⁹ http://www.ct-toolkit.ac.uk/db/documents/Joint_Project_Guidance_on_Pharmacovigilance.pdf

question that the Commission should examine. I suspect that the impetus for change must come from the Commission in providing guidance that would help form a consensus by researchers across all member states on this matter of risk based monitoring for pharmacovigilance.

A new legal platform for Pharmacovigilance ?

42. But does risk based monitoring of pharmacovigilance require a reworking of the Clinical Trial Directive? Taken in isolation, the answer is probably not. Risk based pharmacovigilance can be applied within the scope of the Directive as it currently stands. Furthermore, reworking the Directive as a Regulation will neither be practicable nor beneficial as long as there remains divergence in national laws of member states on the matters of insurance, compensation, data protection and privacy. But the European Commission has already decided that a reworking of the pharmacovigilance requirements of Directive 2001/83/EC may be needed.³⁰ One of the features of this proposed strategy will be to introduce a simplified classification of adverse drug reactions [ADR], removing the current references to conditions of normal use and unexpectedness, and potentially requiring a wider class of ADR to be reported to the competent authority by the marketing authorisation holder according to a new causality test. These proposals will impact primarily on the process for marketing authorisation and safety reporting post marketing authorisation.

Risk-Based Governance Arrangements for all Clinical Trials

43. It has been suggested that academic clinical trials should be removed from the scope of the Directive altogether. A separate, but contentious, question is whether the Clinical Trials Directive should be amended so as to remove the distinction between commercial and non-commercial trials. ECRIN and ESF maintain that the distinction should be abolished. They assert that if a distinction were to be maintained and applied to the regulatory requirements of each, then it would merely serve to create a two tier system in research whereby lower standards are seen to be required for academic research. ESF states that if there is any special provision

³⁰ *EC Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance*, dated 5th December 2007

that must be made, it is to provide technical and organisational assistance to academic sponsors rather than academic studies *per se*. ESF goes further and argues for a risk based approach to regulatory requirements for clinical research founded on a risk classification test with four levels of severity. This proposal goes far beyond the scope of a risk based approach to pharmacovigilance. The two issues must not be confused in this consultation or at any time hereafter. ESF maintains that allocating studies to a particular risk category should determine the necessity of requirements such as the submission to the competent authority, insurance, the need for a sponsor, monitoring of the trial and other matters. ESF states that in research studies with a risk that is similar to standard care, these regulatory requirements should be minimised. The ESF response document seems to suggest that even submission to an ethics committee could be dispensed with in this lowest category of risk.

'Light-Touch' Research Governance versus Patient Protection

44. I oppose the ESF recommendations as they currently stand. These proposals need to be thought out again. ESF confuses and conflates a specific methodological issue, such as a risk based approach to safety reporting in clinical trials, with the wider issue of how best to protect the safety and welfare of the research subject by the imposition of necessary regulatory requirements. There is a tension between seeking ways to generate research data efficiently and the need to secure patient protection. Any clinical research method that is not purely observational constitutes an additional intervention in the care of the patient. Any harm that results to the patient from this additional intervention must be compensated according to national laws or special arrangements. So it is a fallacy to suggest that insurance provision for low risk research can be somehow minimised as an ethical or legal concern. If one accepts that injuries of maximum severity can occur from standard treatments, such as the administration of an injection via a contaminated syringe, then it follows that compensation claims of maximum gravity can still arise from research studies involving treatments approximate to standard care. The need for insurance for the research remains as before. The ESF proposals, and any other proposals that follow this model, appear to overlook the inescapable reality that the legal rights of the research subject are fixed and are not modified according to risk. A violation of any legal right of the subject is a matter of equal gravity no matter what assessment has

been made of the risk profile of the study. Potential violations of data protection rights, compensation rights, the seeking of valid legal consent and applying a valid method for seeking inclusion of patients who lack the capacity to consent for themselves can occur in any type of research study and are not infrequently manifested in protocols that come before ethics committees. So regulatory requirements to safeguard the subject from these abuses need to be maintained. To suggest that such safeguards can be relaxed in some types of clinical research is the correlative of suggesting that academic researchers are somehow immune from making these kinds of errors in the first place.

Flexible Research Governance and Stronger Regulation

45. A more exotic consequence of applying a risk classification to broader research governance requirements is that it might open the way for abuse by the researchers themselves. If it were thought that a favourable classification of risk might lead to exemption from the cost and burden of governance compliance, then the unscrupulous researcher might 'cut corners' in the risk assessment that he makes of the study that is to be proposed. It might lead to a phenomenon of 'cramming', whereby researchers compete to include their study in the most favourable category so as to expedite their own research. The possibilities for abuse outweigh the benefits of the model that ESF currently advocates. Ironically, a new system of flexible research governance arrangements applied according to clinical risk would strengthen the case for 'muscular' regulatory bodies in research that can make an effective risk/benefit assessment, not only of the science and the safety of the subject, but also of the effect of the study arrangements upon the legal rights and fair treatment of the research subject. It follows that any suggestion to remove academic trials from the scope of the Directive must also be rejected. The most important question for researchers is whether a risk based approach to pharmacovigilance can be promoted within the current framework of the Clinical Trials Directive and in a harmonised way for those clinical trials taking place across different member states. A secondary question is whether the scope of the specific modalities can be extended. They should concentrate on those issues first rather than trying to meddle with other governance arrangements intended to protect the research subject.

The Legislative Divide between Academic and Commercial Clinical Trials

46. The question is whether the current classification of clinical trials as commercial or non-commercial is one that should be abolished as serving no benefit to the researcher or to the wider public interest. The current distinction between commercial and non-commercial clinical trials can lead to what is sometimes perceived to be an overly-rigid governance approach by some national competent authorities, and which is felt most keenly in partnership research between academic researchers and industry. The Draft Guidance³¹ issued under the auspices of the 2005 Directive defines a non-commercial trial as that which is conducted without the participation of the pharmaceutical industry. It is a defining characteristic of this type of research that the study should not form part of a development programme for a marketing authorisation of a medicinal product. A characteristic of the sponsor of the non-commercial trial is that it owns the data. A further defining characteristic of the sponsor of non-commercial clinical trial is that no agreements between sponsor and third party should be in place that would enable the data to be used for regulatory or marketing purposes. Support by the pharmaceutical industry in supplying drugs for free or reduced cost or providing limited assistance is permissible and will not result in the loss of the non-commercial classification.

What is the purpose of the Academic/Commercial Divide ?

47. It is necessary to ask whether there is an ethical safeguard to be maintained by retaining the distinction between clinical trials that serve to support marketing authorisations and those which do not. If there is an ethical safeguard then it must be asked whether the need can be met by other means. Marketing authorisations mean the chance of commercial profit for the entity that has ownership of the product. Commercial profit motives can tempt the researcher or sponsor to fraud or to elasticity in the rigour of the research. So there may be a public interest to be served in differentiating categories of clinical trial research dependent upon the chance of

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http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/07_2006/guide_noncommercial_2006_07_27.pdf

commercial benefit to the persons involved in that research. Conversely, the academic researcher might be tempted to fraud or other misconduct in order to satisfy a thirst for reputation or preferment that has no bearing on the commercial value of the drug itself. So the question is not whether the risk of fraud is present in one classification of research but not the other, but rather whether the risk is greater in one classification when compared to the other. An answer could be attempted to this question by recourse to studies on the prevalence of research fraud, but time constraints have precluded me from examining this topic on all but a hypothetical basis.

48. If it can be said that the need to safeguard against fraud or research misconduct is the same no matter whether the clinical trial be commercial or non-commercial, and that the only issue is the risk of misconduct within a particular study or field of studies, then it begs the question as to what is the value in retaining the distinction between commercial and non-commercial drug trials in the first instance. Every study should be subject to governance arrangements that enable fraud or misconduct to be detected irrespective of the fact that data use is involved in support of a marketing authorisation. The only remaining justification for retaining the distinction between commercial and non-commercial studies might lie in a greater risk to public safety associated with the marketing of new drugs when compared to the use of authorised medicinal products. But pharmacovigilance requirements under the 2001 Directive can still be applied on a risk-assessed basis that distinguishes between the first in human study from the study of authorised drug products within established indications. The distinction between commercial and non-commercial trials is not relevant, in itself, to the degree of safety reporting that must be made by the researcher to the sponsor. Nor is the distinction relevant to the level of safety reporting that must be made by the sponsor to the competent authority. It is the limited quantity of safety data about a drug when measured against the potential risk to the subject that determines the level of safety reporting that must be applied in risk-based pharmacovigilance. It is therefore difficult to understand why the distinction between commercial and non-commercial trials should be retained on the basis of the need to safeguard public safety. If my reasoning can be supported by further empirical evidence, then the Commission should consider whether the current

distinction between commercial and non-commercial trials of investigational medicinal products is serving any useful purpose at all.

New Modalities to Combat Research Misconduct

49. If the distinction between commercial and non-commercial trials were to be abolished, then the question is whether the Directives currently provide adequate protection against research misconduct. The current regulatory requirements of the Directives have a potential to impact upon research misconduct and they are applied irrespective of whether the study is academic or commercial. But there is a question as to whether the Directives should be amended to apply additional protections against research misconduct. The non-publication of research data adverse to the commercial or academic interests of the sponsor is one example of a governance issue that is not being adequately addressed at this time. Publication bias is at present left to the research community and the publication editors to resolve by self-regulation. The requirement for sponsors to register clinical trials with national databases is one approach that has been adopted by national governance bodies to try to eliminate reporting bias, and the UK Research Ethics Database is an example of this. The fact that the EudraCT database is historically based on studies proceeding towards marketing authorisation suggests that data voids do exist in European drug registration and reporting. Should the Directives be amended to deal specifically with requirements for the publication and reporting of adverse research data that is not used in the course of a marketing authorisation, from trials that would otherwise be classified as commercial and non-commercial? Any resulting database would have to be optimised for meta-analysis and this may be easier to recommend than to achieve. Is this approach to the problem of research fraud better than retaining a distinction between academic and commercial trials that does not appear to be linked to a clear assessment of a fraud risk?

Specific Modalities as an Aid to the Academic Sponsor not the Trial

50. If the distinction between commercial and non-commercial clinical trials is abolished, then what will become of the specific modalities? The specific modalities are an administrative concession to academic studies as a class rather than a response to a safety risk assessed in an individual study or type of studies. So the question is

whether they must be retained as a support to academic research. This will depend in part upon whether the abolition of the academic/commercial distinction results in a greater ease of collaboration between the public and the private sector in clinical trials research. If partnership research is facilitated in this way, then academic researchers might perhaps be willing to accept that they should adhere to more rigorous governance requirements, akin to those imposed on the sponsors of commercial study, as the price to pay for a more bountiful cooperation with industry in collaborative research. If not, then the specific modalities would have to be recast, not as a tolerance afforded to the non-commercial trial, but rather as an allowance conferred upon the non-commercial sponsor. The question is whether it is necessary to retain the current restriction that specific modalities can only apply where there is no substantial involvement by the pharmaceutical industry. Again I pose the question, what is the Commission trying to achieve by retaining this restriction? If the restriction does not combat research misconduct or benefit public safety in a specific way, then what is the value of it? I should add that my comments in this regard are based once again upon hypothetical conjecture and not upon a detailed research.

Mediating Conflicts of Interest between Academic and Commercial Research

51. Is it fair to prohibit a sponsor of a non-commercial trial from being a party to any agreement that would enable study data to be used to support a regulatory purpose or a marketing authorisation? What is the purpose that the Commission hopes to serve by retaining this prohibition? Unless it goes to the matter of fraud, or research misconduct, the public safety, or some wider public interest, then what is the value of the prohibition? It might be argued that it is necessary to preserve the independence of academic institutions from commercial interference so as to safeguard public confidence in state-sponsored research. However, the financial pressures on state hospitals and universities to secure funding from state sources could also compromise their independence in other ways. There is an undoubted ethical tension between the financial payment to a researcher and his involvement in human subject research upon the success of which his payment depends. Could the matter of financial interests in research outcomes be dealt with by a comprehensive code of practice on disclosures of financial interests by academic researchers working in partnership with industry? Might it be possible to use contractual methods to govern the relationship between academic and industry partners by providing that no

additional payments be received by academic researchers and that all financial benefit is channelled to the institution that they represent³²? Is it really necessary to go as far as some commentators in the United States have suggested, and to implement a presumption that academic researchers should not work in partnership with industry in human subject research unless a compelling reason be shown³³? Insofar as the prohibition in the Guidance places fetters upon the freedom of workers, or a restraint upon trade, then there are grounds for the Commission to re-examine this matter within the overall framework of the Treaty obligations of member states. However, in mainstream scientific research, there is a conflict between the need for the academic to publish the results of the data and the need of the industry partner to prevent publication pending the grant of patent protection. One can foresee that similar problems might arise between academic and industry partners in the context of marketing authorisations for clinical trials. Is there a supervening duty upon academic researchers in state hospitals to publish adverse study data in the public interest that might put them in conflict with the commercial imperatives of industrial partners? Is that sufficient justification for retaining the current prohibition on collaborative working? Or are there other solutions that can be applied to deal with the publication problem? Could codes of practice be issued as to the circumstances in which an urgent publication duty could be raised as a defence in law to any claim that an intellectual property right had been violated or that private commercial information had been misused? Should this publication defence be based not only on public protection grounds, as currently prevails, but also on the wider grounds of the public interest? How would this be defined and should this be supported by a new legislative framework at European level with additional penalties for the non-disclosure of safety data that should otherwise have been made public? Would these solutions take some of the 'sting' out of the notion of public private collaboration in clinical trial research or would they drive a wedge between academics and industry?

³² William T. Carpenter, Jr., James I. Koenig, Graeme Bilbe, and Serge Bischoff .
At Issue: A Model for Academic/Industry Collaboration. Schizophrenia Bulletin, 30(4):997-1004,2004

³³ <http://www.aamc.org/research/coi/firstreport.pdf>

Data Ownership between Academic and Commercial Sponsors

52. If the prohibition on joint working in 'commercially motivated research' were to be abolished, then academic researchers might be able to benefit from the latitude afforded to them under the Directive for the use of multiple sponsors in clinical trials. It follows that an academic sponsor would be able to share the ownership of study data with a commercial co-sponsor. It would be a matter for contractual agreement. The usual prohibitions would apply, as set out under national laws, and which govern the formation of illegal contracts, the infringement of competition laws, or which specify things that cannot be the subject of a patent .
53. The most divisive issue to arise from collaboration between academic researchers and industry is the question of who owns the data and any resulting intellectual property generated by that research. I do not propose to make a detailed examination of the issue in this document but the following observations warrant further examination. Academic partnerships with industry have been a feature of European science and technology research for some time, but there are difficulties. Would public private partnerships in clinical trials benefit from the work that has already been done in formulating guidance for the ownership of intellectual property in mainstream science and technology research? It should be considered whether the work of CREST³⁴ can be applied to the clinical trial sector directly or by necessary modification. In the United Kingdom, so-called Lambert Agreements³⁵ have also been developed to serve as model contract templates for cooperation between academic researchers and businesses. The tension between the need to publish and the need to restrict data pending patent protection or marketing authorisation could be the subject of specific guidance by the Commission or its advisory bodies. CREST contemplates a range of contractual agreements in which ownership rights are scaled between academic and commercial partners and in which the right to information usage and research publication is mediated by means of an agreed period of delay before first publication. Might similar modalities be

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http://ec.europa.eu/research/era/pdf/ipr_eur-20230_en.pdf

³⁵ <http://www.innovation.gov.uk/lambertagreements/index.asp?lv1=2&lv2=1&lv3=0&lv4=0>

applied to clinical trial research , but subject to a public health or public interest defence for early publication ?

Summary of Conclusions

- ✓ Merge the ethics committee and competent authority into a single regulatory body for clinical trials in member states. This independent regulatory body would provide scientific, safety and ethical review and would also provide better protection for the legal rights of the subject at or before the point at which research commences. Application processing time could speed up and the number of separate approvals would be reduced. Safety reporting in pharmacovigilance would be simplified . Could there be a similar system of regulatory governance at European level for centralised permissions?
- ✓ A new legal framework of rights for human s in bio-medical research is needed to support this new regulatory system and to improve harmonisation between member states in research activity .
- ✓ Governance of health information in research means that issues in the EC Consultation on the Clinical Trials Directive are relevant to the current EC Consultation on the Data Directive. Common issues should be considered under each Consultation . Can reforms of commercial data processing rules be applied also to the bio-medical research sector?
- ✓ Reform of the Data Directive is needed to make it adaptive and reflexive using privacy tools based on risk assessment . Redraft the 'research exemption' to make it intelligible to medical workers. Reform UK Information Governance in bio -medical research by providing a unified regulatory system for control of health information in research. Merge the ethics committee into a new regulator for health information in research. New legal platforms for data protection could facilitate multi -national database research for cancer registries and public health .
- ✓ Legal solutions need to be applied to make research 'global'. Consider the use of contractual legal solutions to promote collaborative research based on OECD Standard Contractual Clauses and Binding Corporate Rules for data processing.

Consider the efficacy of contractual schemes for compensation for subjects in research provided by means of risk-based 'block' purchasing of insurance by research collaborations .

- ✓ A risk-based approach to research governance should be encouraged where patient safety is not put at risk. Risk-Based Pharmacovigilance means flexible safety reporting rules based on the nature of the study, safety risk, and the relevance of adverse events to study outcomes. Common agreements between member states are needed for this. Specific Modalities may be a limited option in comparison.
- ✓ There is a potential conflict between 'light-touch' research governance and patient protection. Beware extending risk-based assessment to other governance requirements such as sponsorship and insurance . It is wrong to assume that research approximate to standard care has lower risks. So insurance and other patient legal protections need to be maintained. Legal protection for the human in research cannot be disabled for the comfort of the researcher.
- ✓ The Directive's distinction between academic and commercial clinical trial research , and the prohibition in the Draft Guidance on co-working in 'commercially motivated research', both need to be re-examined to determine whether they are justified in the public interest. Would the use of financial interest disclosure rules, or contracts to limit profit-taking by academic researchers, remove some of the ethical obstacles to public-private partnership in clinical trials? Can legal solutions be applied to combat misconduct or commercially motivated bias in research, such as legal and professional duties on the researcher to publish all adverse findings or report adverse data by recourse to a new public interest defence? New arrangements for the ownership of data and intellectual property arising from academic and commercial co-sponsorship would have to be devised for the clinical trials sector.

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Christopher Roy-Toole